Effective Health Care

Diagnosing and Staging Lung Cancer

Results of Topic Selection Process & Next Steps

The nominator, the American College of Chest Physicians (CHEST), is interested in a new evidence review on diagnosing and staging lung cancer to inform the update of their 2013 guidelines. Due to limited program resources, the program is unable to develop a review at this time. No further activity on this nomination will be undertaken by the Effective Health Care (EHC) Program.

Topic Brief

Topic Name: Diagnosing and Staging Lung Cancer

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Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Summary

- This nomination meets all selection criteria.
- Forty-three completed studies and one in-process study were identified on this topic. Over half of these studies examined either performance characteristics or patient outcomes associated with one particular staging modality (EBUS-TBNA).

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Background

Lung cancer is the second most common type of cancer and the leading cause of cancer death in the United States.[1] A variety of tools are used to diagnosis and stage lung cancer. Patients with suspected lung cancer first receive a PET or CT, which confirms the location and size of a mass. A bronchoscopy (conventional, flexible, electromagnetic navigation-guided, or radial endobronchial ultrasound-guided) may then be used to provide images of the mass and to collect samples for histological testing. Other surgical tools may be used to collect samples in the lungs or pleural cavity without imaging (i.e., transthoracic needle aspiration biopsy, pleural biopsy). Staging of lung cancer assesses the extent to which the cancer has spread beyond the primary tumor. Staging is completed at the same time as diagnosis, and involves using similar tools (PET, CT, endobronchial ultrasound-guided needle aspiration; endoscopic ultrasound-guided needle aspiration, video-assisted thoracoscopic surgery) to look beyond the lungs- especially the mediastinum- to determine where cancer has spread.

Although many tools are available to diagnosis and stage lung cancer, the optimal combination and sequence of tools is unclear. A review on the performance characteristics and effects of each of these tools, used alone or in combination, on the need for subsequent testing, prognosis, under- or over-treatment, and patient outcomes would better inform clinical decision-making and facilitate the appropriate use of tools.

Nominator and Stakeholder Engagement: CHEST originally nominated one topic on diagnosing lung cancer and one topic on staging non-small cell lung cancer. After consultation with a local topic expert as well as a discussion with the nominator, the diagnosis and staging topics were combined into a single nomination. This is because the same tools are used for diagnosis and screening, the process of diagnosis and staging are completed at the same time, and there is considerable overlap in the literature. In addition, the key questions and PICOs for this topic were re-scoped to better reflect clinical decision-making.

The key questions for this nomination are:

1. Among adults with suspected lung cancer, what are the performance characteristics and effects of each diagnosis/staging tool on the need for subsequent testing, prognosis, treatment, and patient outcomes?
    a. CT scan
    b. PET scan
    c. Pleural biopsy (closed image guided or thoracoscopic)
    d. Flexible bronchoscopy
    e. R-EBUS bronchoscopy
    f. EMN bronchoscopy
    g. TTNA of lung airways or mediastinum
    h. Cervical and extended cervical mediastinoscopy
    i. EUS-NA of the mediastinum
    j. EBUS-NA of the mediastinum
    k. VATS of the mediastinum
    l. TBNA of the mediastinum

2. Among adults with suspected lung cancer, what are the performance characteristics and effects of a) dual-modality or b) tri-modality compared to single-modality staging on the need for subsequent testing, prognosis, treatment, and patient outcomes?

3. Among adults who undergo diagnosis and staging for suspected lung cancer, does the sequence of invasive testing affect the total number of tests, their complications, or their

performance characteristics?

4. Among adults who undergo diagnosis and staging for suspected lung cancer, do performance characteristics and outcomes vary by patient characteristics, including:
    a. Age/comorbidities
    b. Suspected stage of cancer (especially early vs. advanced)
    c. Willingness and ability to complete treatment

To define the inclusion criteria for the key questions we specify the population, interventions, comparators, and outcomes (PICOs) of interest (Table 1).

Table 1. Key Questions and PICOs

Key Question	1. Among adults with suspected lung cancer, what are the performance characteristics and effects of each diagnosis/staging tool on the need for subsequent testing, prognosis, treatment, and patient outcomes?	2. Among adults with suspected lung cancer, what are the performance characteristics and effects of a) dual-modality or b) tri-modality compared to single-modality staging on the need for subsequent testing, prognosis, treatment, and patient outcomes?	3. Among adults who undergo diagnosis and staging for suspected lung cancer, does the sequence of invasive testing affect the total number of tests, their complications, or their performance characteristics?	4. Among adults who undergo diagnosis and staging for suspected lung cancer, do performance characteristics and outcomes vary by patient characteristics, including: a. Age/comorbidities b. Suspected stage of cancer (especially early vs. advanced) c. Willingness and ability to complete treatment
Population	Adults who are initially suspected of having lung cancer	Adults who are initially suspected of having lung cancer	Adults who are initially suspected of having lung cancer who undergo diagnosis and staging	Adults who are initially suspected of having lung cancer who undergo diagnosis and staging
Intervention	a. CT scan b. PET scan c. Pleural biopsy (closed image guided or thoracoscopic) d. Flexible bronchoscopy e. R-EBUS bronchoscopy f. EMN bronchoscopy g. TTNA of lung airways or mediastinum h. Cervical and extended cervical mediastinoscopy i. EUS-NA of the mediastinum j. EBUS-NA of the mediastinum k. VATS of the mediastinum l. TBNA of the mediastinum	a. Dual-modality staging (CT plus PET scans, or CT scan plus invasive staging [mediastinoscopy or R-EBUS, EUS-NA, VATS, TTNA, TBNA of the mediastinum]) b. Tri-modality staging (CT, PET, and invasive staging [mediastinoscopy or R-EBUS, EUS-NA, VATS, TTNA, TBNA of the mediastinum])	2 or more diagnostic/staging tools from KQ1	1 or more diagnostic/staging tools from KQ1
Comparator	Other diagnostic/staging tool or reference standard (surgical biopsy)	Use of 1 staging tool alone	Alternative sequence of the same diagnostic/staging tools	Other diagnostic/staging tool or reference standard (surgical biopsy)
Outcome	• Negative/positive predictive value • Need for subsequent testing • Prognosis • Under or over-treatment • Patient outcomes (adverse events from procedure, quality of life, mortality)	• Negative/positive predictive value • Need for subsequent testing • Prognosis • Under or over-treatment • Patient outcomes (adverse events from procedure, quality of life, mortality)	• Negative/positive predictive value • Need for subsequent testing • Prognosis • Under or over-treatment • Patient outcomes (adverse events from procedure, quality of life, mortality)	• Negative/positive predictive value • Need for subsequent testing • Prognosis • Under or over-treatment • Patient outcomes (adverse events from procedure, quality of life, mortality)

Abbreviations: CT=Computerized tomography; EBUS-NA= Endobronchial ultrasound-guided needle aspiration; EUS-NA= Endoscopic ultrasound-guided needle aspiration; NSCLC= non-small cell lung cancer; PET= Positron emission tomography; R-EBUS= radial endobronchial ultrasound; TBNA= Transbronchial needle aspiration cytology; TTNA= Transthoracic needle aspiration; VATS=Video-assisted thoracoscopic surgery

Methods

We assessed nomination *0767/0768 Diagnosing and Staging Lung Cancer* for priority for a systematic review or other AHRQ EHC report with a hierarchical process using established selection criteria (Appendix A). Assessment of each criteria determined the need for evaluation of the next one.

1. Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. Establish the overall *importance* of a potential topic as representing a health or healthcare issue in the United States.
3. Determine the *desirability of new evidence review* by examining whether a new systematic review or other AHRQ product would be duplicative.
4. Assess the *potential impact* a new systematic review or other AHRQ product.
5. Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years on the key questions of the nomination. See Appendix B for sources searched.

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

We conducted a literature search in PubMed from April 2013 to April 2018.

We reviewed all (n=241) identified titles and abstracts for inclusion and classified identified studies by study design, to assess the size and scope of a potential evidence review.

See Appendix C for the PubMed search strategy and links to the ClinicalTrials.gov search.

Value

We assessed the nomination for value. We considered whether or not the clinical, consumer, or policymaking context had the potential to respond with evidence-based change; and if a partner organization would use this evidence review to influence practice.

Compilation of Findings

We constructed a table with the selection criteria and our assessments (Appendix A).

Results

Appropriateness and Importance

This is an appropriate and important topic. Approximately six percent of people will be diagnosed with lung and bronchus cancer in their lifetime, making it the second most common type of cancer.[1] Lung cancer is also the leading cause of cancer death in the United States.[1] There are many tests for diagnosing and staging lung cancer, and the selection of the right tests and sequence has a major impact on how accurately and efficiently a patient's true diagnosis

and stage are reached. In addition, there are a wide variety of treatment options based on a patient's diagnosis and stage. Basing treatment decisions on an inaccurate diagnosis or stage may lead to poor health outcomes as well as increased health care costs.

Desirability of New Review/Duplication

A new evidence review on diagnosing and staging lung cancer would not be duplicative of an existing product. We identified 2 completed[2, 3] and 1 in-process[4] systematic reviews (SRs) that partially addressed the key questions of interest.

One 2016 SR and meta-analysis examined the prognostic value of combined PET/CT staging for patients with surgical non-small cell lung cancer (KQ1a, KQ1b).[2] Another 2016 SR and meta-analysis examined the diagnostic accuracy (including negative predictive value) of EBUS-NA, EUS-NA or a combined approach for patients with non-small cell lung cancer (KQ1i, KQ1j) and assessed whether the accuracy varied by the sequence in which EBUS-NA and EUS-NA were delivered (KQ3).[3] One in-process review will look at the use of ultrasound characteristics from staging EBUS to predict malignancy (KQ1j).[4] None of these reviews covered all outcomes of interest for a particular sub-question (i.e., positive and negative predictive values, need for subsequent testing, prognosis, under or over-treatment, adverse events from procedure, quality of life, and mortality).

See Table 2, Duplication column.

Impact of a New Evidence Review

A new systematic review on diagnosing and staging lung cancer may have high impact. CHEST last released guidelines on the diagnosis of lung cancer[5] in 2013 (last search 2011) and staging of non-small lung cancer[6] in 2013 (last search 2012). All recommendations for diagnosis and staging were based on moderate or low-quality evidence. This indicates that a new systematic review summarizing new evidence on this topic has the potential to inform guidance.

There is also practice variation in the diagnosis and staging of lung cancer, indicating there is an implementation gap in addition to an information gap. According to the SEER registry, only 30% of lung cancer patients receive bi-modality staging and 5% receive tri-modality staging, despite recommendations that at least two staging modalities be used.[7]

Feasibility of a New Evidence Review

A new evidence review on diagnosing and staging lung cancer is feasible. We identified a total of 43 completed and one in-process studies addressing this topic. An evidence review would likely be medium-sized. Although fewer than 50 studies were identified, further refinement of the key questions and PICOs are needed, which would likely result in the inclusion of additional studies.

A total of 40 completed studies addressed Key Question 1.[8-47] Most of these studies examined the use of EBUS-TBNA in mediastinal staging (KQ1j, KQ1l). Of the remaining studies, most examined a combination of tools, such as PET/CT. One additional in-process study[48] will examine the positive predictive value of high-definition video bronchoscopy for detecting malignancies.

One study addressed Key Question 2.[49] This study examined PET/CT with EBUS-TBNA versus PET/CT alone to evaluate patients with non-small cell lung cancer prior to stereotactic ablative body radiotherapy.

Two retrospective studies addressed Key Question 3.[27, 50] One study examined whether mediastinal lymph node sampling was conducted as the first invasive procedure in patients with suspected lung cancer and whether this impacted the number of invasive tests performed as

well as complications.[27] A second study examined the number of procedures conducted and time to diagnose lung cancer in a cohort of lung cancer patients.[50]

Two studies addressed Key Question 4.[46, 51] Both studies were conducted in elderly populations, one examined performance characteristics and complications[46] and one only examined complications of EBUS-TBNA.[51]

See Table 2, Feasibility column.

Table 2. Key questions and Results for Duplication and Feasibility

Key Question	Duplication (03/2015-03/2018)	Feasibility (04/2013-04/2018)
KQ 1: Performance characteristics and effects of each diagnostic tool, including: a) CT scan b) PET scan c) Pleural biopsy (closed image guided or thoracoscopic) d) Flexible bronchoscopy e) R-EBUS bronchoscopy f) EMN bronchoscopy g) TTNA of lung airways or mediastinum h) Cervical and extended cervical mediastinoscopy i) EUS-NA of the mediastinum j) EBUS-NA of the mediastinum k) VATS of the mediastinum l) TBNA of the mediastinum	Total number of identified systematic reviews: 3 a) 1 SR[2] b) 1 SR[2] c) None d) None e) None f) None g) None h) None i) 2 SR[3, 4] j) 1 SR[3] k) None l) None	Size/scope of review Relevant Studies Identified: 40 a) 2 prospective cohort[8, 47] and 3 retrospective cohort[9-11] b) 3 prospective cohort[8, 12, 47] and 3 retrospective cohort[9, 10, 13] c) None d) 1 retrospective cohort[14] e) 2 prospective cohort[15, 16] f) None g) None h) 1 prospective cohort[17] i) 2 prospective cohort[12, 18] j) 1 RCT,[19] 9 prospective cohort, [8, 17, 20-26, 45] 18 retrospective cohort, [11-13, 18, 27-41] 2 surveys[42, 43] k) 1 prospective trial[44] l) 1 RCT,[19] 10 prospective cohort, [8, 15, 17, 20-26, 45] 15 retrospective cohort,[11, 27-40] 2 surveys[42, 43] Clinicaltrials.gov • Recruiting: None • Active: 1[48] • Complete: None
KQ 2: Among adults with suspected lung cancer, what are the performance characteristics and effects of a) dual-modality or b) tri-modality compared to single-modality staging on the need for subsequent testing, prognosis, treatment, and patient outcomes?	Total number of identified systematic reviews: None a) None b) None	Size/scope of review Relevant Studies Identified: 1 a) 1 retrospective cohort[49] b) None Clinicaltrials.gov • Recruiting: None • Active: None • Complete: None
KQ 3. Among adults who undergo diagnosis and staging for suspected lung cancer, does the sequence of invasive testing affect the total number of tests, their complications, or their performance characteristics?	Total number of identified systematic reviews: 1 • 1 SR[3]	Size/scope of review Relevant Studies Identified: 2 ○ 2 retrospective cohort[27, 50] Clinicaltrials.gov • Recruiting: None • Active: None • Complete: None

Key Question	Duplication (03/2015-03/2018)	Feasibility (04/2013-04/2018)
KQ 4: Among adults who undergo diagnosis and staging for suspected lung cancer, do performance characteristics and outcomes vary by patient characteristics, including: a) Age/comorbidities b) Suspected stage of cancer (especially early vs. advanced) c) Willingness and ability to complete treatment	Total number of identified systematic reviews: None a) None b) None c) None	Size/scope of review Relevant Studies Identified: 2 • 1 prospective cohort[46] and 1 retrospective cohort[51] Clinicaltrials.gov • Recruiting: None • Active: None • Complete: None

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; CT=Computerized tomography; EBUS-NA= Endobronchial ultrasound-guided needle aspiration; EUS-NA= Endoscopic ultrasound-guided needle aspiration; KQ=Key Question; NSCLC= non-small cell lung cancer; PET= Positron emission tomography; R-EBUS= radial endobronchial ultrasound; TBNA= Transbronchial needle aspiration cytology; TTNA= Transthoracic needle aspiration; VATS=Video-assisted thoracoscopic surgery

Value

The potential for value of a new systematic review is high, as this topic exists within a clinical context that is amenable to evidence-based change and CHEST plans to use an evidence review to inform the update of their 2013 guidelines.

Summary of Findings

- Appropriateness and importance: The topic is both appropriate and important.
- Duplication: A new review would not be duplicative of an existing product. We identified 2 completed and 1 in-process systematic reviews that partially addressed the key questions of interest. However, none of these reviews covered all outcomes of interest for a particular sub-question.
- Impact: A new systematic review has high impact potential. CHEST last released guidelines on the diagnosis of lung cancer in 2013 (last search 2011) and staging of non-small lung cancer in 2013 (last search 2012). All recommendations were based on low or moderate-quality evidence, indicating there is an information gap that could be informed by a new systematic review.
- Feasibility: A new review is feasible. Forty-three completed studies and one in-process study were identified, indicating the evidence base is medium-sized.
    - KQ1: Forty completed studies and one in-process study addressed KQ1. The majority of studies examined performance characteristics and outcomes associated with EBUS-TBNA for mediastinal staging (KQ1i, KQ2l).
    - KQ2: One study addressed KQ2. This study examined PET/CT with EBUS-TBNA versus PET/CT alone to evaluate patients with non-small cell lung cancer prior to stereotactic ablative body radiotherapy.
    - KQ3: Two studies addressed KQ3. One study examined the impact of mediastinal lymph node sampling as the first invasive staging procedure, and a second study assessed the number of procedures conducted and time to diagnose lung cancer.
    - KQ4: Two studies addressed KQ4, both of which examined complications associated with EBUS-TBNA in older people.
- Value: The potential for value is high, as CHEST plans to use a new evidence review to inform their 2013 guidelines on establishing the diagnosis of lung cancer and staging non-small cell lung cancer.

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Appendix A. Selection Criteria Summary

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes, the nomination represents diagnostic and staging modalities that are available in the United States.
1b. Is the nomination a request for a systematic review?	Yes, this is a request for a systematic review.
1c. Is the focus on effectiveness or comparative effectiveness?	Yes, the focus is on the performance characteristics and other outcomes associated with the use of each of these modalities, compared to each other or a reference standard.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes, the nomination is consistent with what is known about the topic.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Yes, lung cancer is the second most common type of cancer and the leading cause of cancer death in the United States.[1]
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes, due to the large prevalence and low survival rate, this topic is of high public interest.
2c. Represents important uncertainty for decision makers	Yes, this nomination represents important uncertainty for decision-makers. There are many tests for diagnosis and staging, and the selection of the right tests and sequence has a major impact on how accurately and efficiently a patient's true diagnosis and stage are reached. In addition, there are a wide variety of treatment options based on a patient's diagnosis and stage. Basing treatment decisions on an inaccurate diagnosis or stage may lead to poor outcomes.
2d. Incorporates issues around both clinical benefits and potential clinical harms	Yes, both benefits and harms of diagnosis and staging are incorporated into this nomination.
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes, this nomination represents high costs. In Spain, the average cost of diagnosing and treating lung cancer is at least $16,000, depending on the stage.[52] Costs could potentially be reduced through the reduction of unnecessary tests.
3. Desirability of a New Evidence Review/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	A new evidence review would not be duplicative of an existing product. We identified 2 completed[2, 3] and 1 in-process[4] systematic reviews that partially addressed the key questions of interest. One 2016 SR and meta-analysis examined the prognostic value of combined PET/CT staging for patients with surgical non-small cell lung cancer (KQ1a, KQ1b).[2] Another 2016 SR and meta-analysis examined the diagnostic accuracy (including negative predictive value)

	of EBUS-NA, EUS-NA or a combined approach for patients with non-small cell lung cancer (KQ1i, KQ1j) and assessed whether the accuracy varied by the sequence in which EBUS-NA and EUS-NA were delivered (KQ3).[3] One in-process review will look at the use of ultrasound characteristics from staging EBUS to predict malignancy (KQ1j).[4] None of these reviews covered all outcomes of interest for a particular sub-question.
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	CHEST last released guidelines on the diagnosis of lung cancer[5] in 2013 (last search 2011) and staging of non-small lung cancer[6] in 2013 (last search 2012). All recommendations for diagnosis were 1B or 1C, while all recommendations for staging were 1B, 1C, or 2B. In summary, all recommendations for diagnosing and staging lung cancer are based on moderate or low-quality evidence. This indicates that a new systematic review on this topic has the potential to inform guidance.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	There is practice variation. According to the SEER registry, only 30% of lung cancer patients receive bi-modality staging and 5% receive tri-modality staging, despite recommendations that at least 2 staging modalities be used.[7] This indicates there is an implementation gap, in addition to an information gap.
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	A new evidence review is feasible. We identified a total of 43 completed and 1 in-process studies addressing this topic. An evidence review would likely be medium-sized. Although fewer than 50 studies were identified, further refinement of the key questions and PICOs are needed, which would likely result in the inclusion of additional studies. A total of 40 completed studies addressed Key Question 1.[8-47] The majority of these studies examined the use of EBUS-TBNA in mediastinal staging (KQ1j, KQ1l). Of the remaining studies, most examined a combination of tools, such as PET/CT. One study directly addressed Key Question 2.[49] This study examined PET/CT with EBUS-TBNA versus PET/CT alone to evaluate patients with non-small cell lung cancer prior to stereotactic ablative body radiotherapy. Two retrospective studies directly addressed Key Question 3.[27, 50] One study examined whether mediastinal lymph node sampling was conducted as the first invasive procedure in patients with suspected lung cancer and whether this impacted the number of invasive

	tests performed as well as complications.[27] A second study examined the number of procedures conducted and time to diagnose lung cancer in a cohort of lung cancer patients.[50] Two studies directly addressed Key Question 4.[46, 51] Both were conducted in elderly populations, one examined performance characteristics and complications[46] and one only examined complications of EBUS-TBNA.[51] *ClinicalTrials.gov*. One in-process study[48] will examine the positive predictive value of high-definition video bronchoscopy for detecting malignancies.
6. Value	
6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change	Yes, this topic exists within a clinical context that is amenable to evidence-based change.
6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)	Yes, CHEST plans to use an evidence review to inform the update of their 2013 guidelines on lung cancer diagnosis and staging.

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; CHEST= American College of Chest Physicians; CT=Computerized tomography; KQ=Key Question; EBUS-NA= Endobronchial ultrasound-guided needle aspiration; EUS-NA= Endoscopic ultrasound-guided needle aspiration; NSCLC= non-small cell lung cancer; PET= Positron emission tomography; SEER= Surveillance, Epidemiology and Results Program of National Cancer Institute; TBNA= Transbronchial needle aspiration cytology

Appendix B. Search for Evidence Reviews (Duplication)

Listed are the sources searched.

Search date: March 2015 to March 2018
AHRQ: Evidence reports and technology assessments, USPSTF recommendations
VA Products: PBM, and HSR&D (ESP) publications, and VA/DoD EBCPG Program
Cochrane Systematic Reviews and Protocols http://www.cochranelibrary.com/
PubMed
PubMed Health http://www.ncbi.nlm.nih.gov/pubmedhealth/
HTA (CRD database): Health Technology Assessments http://www.crd.york.ac.uk/crdweb/
PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/
CADTH (Canadian Agency for Drugs and Technologies in Health) https://www.cadth.ca/
DoPHER (Database of promoting health effectiveness reviews) http://eppi.ioe.ac.uk/webdatabases4/Intro.aspx?ID=9
ECRI institute https://www.ecri.org/Pages/default.aspx
PsycINFO (Ovid)

Appendix C. Search Strategy & Results (Feasibility)

Diagnosis and Screening for Lung Cancer MEDLINE(PubMed) April 4th, 2018	
Concept	Search String
Lung Cancer	(("Lung Neoplasms/classification"[Mesh] OR "Lung Neoplasms/diagnosis"[Mesh] OR "Lung Neoplasms/diagnostic imaging"[Mesh] OR "Lung Neoplasms/pathology"[Mesh]))) OR ((lung[Title/Abstract]) AND (cancer[Title/Abstract] OR cancers[Title/Abstract] OR neoplasm[Title/Abstract] OR neoplasms[Title/Abstract] OR carcinoma[Title/Abstract] OR carcinomas[Title/Abstract]))
AND	
Diagnosis	(("Diagnosis"[Mesh] OR "diagnosis" [Subheading] OR "Early Detection of Cancer"[Mesh] OR "Early Diagnosis"[Mesh])) OR ((diagnosis[Title/Abstract] OR dx[Title/Abstract]))
OR	
Staging	("Neoplasm Staging"[Mesh]) OR (("neoplasm staging"[Title/Abstract] OR "cancer staging"[Title/Abstract]))
AND	
Specific Interventions (OR)	
CT Scan	((("ct scan"[Title/Abstract] OR "computed tomography"[Title/Abstract])) OR "Tomography, X-Ray Computed"[Mesh]
PET Scan	((("PET Scan"[Title/Abstract] OR "positron Emission tomography"[Title/Abstract])) OR "Positron Emission Tomography Computed Tomography"[Mesh]
Pleural Biopsy	((Pleural Biopsy[Title/Abstract]) OR "Biopsy"[Mesh])
Flexible bronchoscopy	("Bronchoscopy"[Mesh]) OR Flexible bronchoscopy[Title/Abstract]
R-EBUS bronchoscopy	("Bronchoscopy"[Mesh]) OR (("R-EBUS bronchoscopy"[Title/Abstract]) OR

	"Endobronchial Ultrasound Bronchoscopy"[Title/Abstract])
EMN bronchoscopy	("Bronchoscopy"[Mesh]) OR (("Electromagnetic Navigation Bronchoscopy"[Title/Abstract]) OR EMN bronchoscopy[Title/Abstract])
TTNA of lung airways or mediastinum	("Biopsy, Fine-Needle"[Mesh]) OR (("Image guided transthoracic needle aspiration"[Title/Abstract]) OR TTNA[Title/Abstract])
Cervical and extended mediastinoscopy	(mediastinoscopy[Title/Abstract]) OR "Mediastinoscopy"[Mesh]
EUS-NA of the mediastinum	((("endoscopic ultrasound-guided needle aspiration"[Title/Abstract]) OR EUS-NA[Title/Abstract])) OR "Endoscopic Ultrasound-Guided Fine Needle Aspiration"[Mesh]
EBUS-NA of the mediastinum	((("Endobronchial ultrasound"[Title/Abstract]) OR EBUS-NA[Title/Abstract])) OR "Ultrasonography"[Mesh]
VATS of the mediastinum	((("Video-assisted thoracoscopic surgery"[Title/Abstract]) OR VATS[Title/Abstract])) OR "Thoracic Surgery, Video-Assisted"[Mesh]
TBNA of the mediastinum	("Endoscopic Ultrasound-Guided Fine Needle Aspiration"[Mesh]) OR (("transbronchial needle aspiration"[Title/Abstract]) OR TBNA[Title/Abstract])
NOT Editorials, etc.	(((((letter[Publication Type]) OR news[Publication Type]) OR patient education handout[Publication Type]) OR comment[Publication Type]) OR editorial[Publication Type]) OR newspaper article[Publication Type]
Limit to last 5 years ; human ; English ; Adult	Filters activated: published in the last 5 years, Humans, English, Adult: 19+ years
N=241	
Systematic Reviews N=3	PubMed subsection “Systematic[sb]”
https://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/54683547/public/	

Randomized Controlled Trials N=37	Cochrane Sensitive Search Strategy for RTCs
https://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/54683572/public/	
Other N=201	
https://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/54690645/public/	

ClinicalTrials.gov searched on March 4th, 2018
76 Studies found for: diagnosis OR staging | *Completed Studies* | Lung Neoplasms | Adult, Senior | Start date from 01/01/2013 to 12/31/2018
https://clinicaltrials.gov/ct2/results?cond=Lung+Neoplasms&term=diagnosis+OR+staging&type=&rslt=&recrs=e&age_v=&age=1&age=2&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&strd_s=01%2F01%2F2013&strd_e=12%2F31%2F2018&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&lupd_s=&lupd_e=

54 Studies found for: diagnosis OR staging | *Active, not recruiting Studies* | Lung Neoplasms | Adult, Senior | Start date from 01/01/2013 to 12/31/2018
https://clinicaltrials.gov/ct2/results?cond=Lung+Neoplasms&term=diagnosis+OR+staging&type=&rslt=&recrs=d&age_v=&age=1&age=2&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&strd_s=01%2F01%2F2013&strd_e=12%2F31%2F2018&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&lupd_s=&lupd_e=